PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference A2039-7003WO.	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/087417	International filing date *(day/month/year)* 13 December 2007 (13.12.2007)	Priority date *(day/month/year)* 18 December 2006 (18.12.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALTUS PHARMACEUTICALS INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 23 June 2009 (23.06.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Beate Giffo-Schmitt e-mail: pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/087417	13.12.2007	18.12.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/10 A61K38/27

Applicant
ALTUS PHARMACEUTICALS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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Date of completion of this opinion
see form PCT/ISA/210

Authorized Officer

Epskamp, Stefan

Telephone No. +31 70 340-2857

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/087417

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 55-64

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 55-64

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7, 8, 12, 13, 16, 22, 26-29, 32, 33, 37, 38, 41, 45, 46, 49, 52, 53, 67, 72, 73, 77, 83, 99, 100, 102-123
	No:	Claims	1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124, 125
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54, 65-125
Industrial applicability (IA)	Yes:	Claims	1-54, 65-125
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 55-64 have not been searched, as they do not fulfill the requirements of Rule 39.1 PCT. The claimed methods merely appear to relate to methods of doing business (Rule 39.1(iii)) and/or presenting information (Rule 39.1(v)).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: WO 2004/060310 A
D2: WO 92/00998 A
D3: WO 93/12812 A

Clarity, Support

1 - Claims 1 and 30 appear to lack essential features, as they define preparations comprising "one or more" of a list of ingredients. It would appear that for instance in claim 1, selecting only the suspending agent does not solve any problem the applicant set out to solve. As such, these claims are unclear, and cannot be seen as being supported by the description (Article 6 PCT).

2 - Claim 1 further lacks clarity and support, as the wording "polyelectrolyte complexed recombinant human growth hormone or human growth hormone derivative crystals" is unclear. The present wording suggests that as hGH two alternatives could be chosen, namely "polyelectrolyte complexed recombinant human growth hormone" or "human growth hormone derivative crystals". This does not appear to correspond to what is described in the description (see e.g. page 2, lines 28-30; page 14, lines 20-26; page 54, lines 23-28), leading to a lack of clarity and support (Article 6 PCT). A similar objection applies to claim 27.

3 - Adding to the lack of clarity, the term "derivative" in independent claims 1, 27 and 85 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Also the definition of this term on page 16, line 15 ff of the description, is unclear. It is unclear what is meant by a "protein that differs by at

least x % from the amino acid sequence of" hGH.
Consequently the subject-matter of claims 1, 27 and 85 does not fulfil the requirements of Article 6 PCT.
4 - The term "salt buffer", used e.g. in claim 1, is not a generally recognised term, and as such unclear (Article 6 PCT).
5 - In claim 66, the preparation of crystallized protein of claim 65 is defined as a "solution of crystals". This feature is contradictory, as a solution does not contain crystals of the dissolved compound. The same objection applies to claims 75 and 76. Claims 65, 66, 75 and 76 therefore lack clarity (Article 6 PCT).
6 - In claim 85 a lyophilized preparation is defined by its composition after resuspension. Such a definition is unclear (Article 6 PCT), as it does not define the actual lyophilized preparation. Similarly, the preparations of claims 102-123 are defined in terms of the concentration of ingredients after reconstitution. The concentrations defined cannot apply to the lyophilized preparation, leading to a lack of clarity (Article 6 PCT).

Novelty

1 - Furthermore, the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124 and 125 is not new in the sense of Article 33(2) PCT, and therefore the criteria of Article 33(1) PCT are not met.
2 - Document D1 (§§ 12-14; §§ 80-83; examples; claims) discloses crystals of human growth hormone (derivative), complexed to e.g. protamine or polyarginine, and compositions for injection comprising the crystals. A preferred formulation vehicle comprsies 100 mM sodium acetate, 5% PEG6000, 25 mM Tris.HCl, pH 7.5 (see § 83), but other formulations are foreseen (§ 82; examples 22, 25). The incorporation of the compositions in pre-filled syringes, infusion pumps and needle-free injectors is also foreseen (see e.g. § 80)
With respect to D1, claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81 and 84 are considered to lack novelty.
3 - Document D2 (examples 6-10; claims) and D3 (examples 7-10; examples) disclose the preparation of hGH crystals. After preparation the crystals are freeze-dried to achieve dry crystals, from which a pharmaceutical suspension is made. The freeze-dried crystals cannot be distinguished from the lyophilized preparation of claim 85, as they could indeed

be resuspended in a composition comprising a buffer, a salt and PEG.
Consequently, claims 85-98, 101, 124 and 125 are considered to lack novelty over D2 and D3.

Inventive Step

1 - Lacking novelty, claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124 and 125 cannot be considered inventive (Article 33(4) PCT).

2 - Also in view of the clarity objections raised above, independent claims 27, 52, 53, 99, 100, 102-123 and dependent claims 7, 8, 12, 13, 16, 22, 26, 28, 29, 32, 33, 37, 38, 41, 45, 46, 49, 67, 72, 73, 77, 83 cannot be considered inventive. The features presented in these claims are a combination of features obvious to the skilled person in consideration of documents D1-D3, or they concern minor modifications which lie within the normal practice of the skilled person.

Industrial applicability

Claims 1-54 and 65-125 fulfill the rquirements of Article 33(4) PCT.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/087417	13.12.2007	18.12.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/10 A61K38/27

Applicant
ALTUS PHARMACEUTICALS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Date of completion of this opinion
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/087417

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 55-64

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 55-64

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7, 8, 12, 13, 16, 22, 26-29, 32, 33, 37, 38, 41, 45, 46, 49, 52, 53, 67, 72, 73, 77, 83, 99, 100, 102-123
	No:	Claims	1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124, 125
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54, 65-125
Industrial applicability (IA)	Yes:	Claims	1-54, 65-125
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 55-64 have not been searched, as they do not fulfill the requirements of Rule 39.1 PCT. The claimed methods merely appear to relate to methods of doing business (Rule 39.1(iii)) and/or presenting information (Rule 39.1(v)).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: WO 2004/060310 A
D2: WO 92/00998 A
D3: WO 93/12812 A

Clarity, Support

1 - Claims 1 and 30 appear to lack essential features, as they define preparations comprising "one or more" of a list of ingredients. It would appear that for instance in claim 1, selecting only the suspending agent does not solve any problem the applicant set out to solve. As such, these claims are unclear, and cannot be seen as being supported by the description (Article 6 PCT).

2 - Claim 1 further lacks clarity and support, as the wording "polyelectrolyte complexed recombinant human growth hormone or human growth hormone derivative crystals" is unclear. The present wording suggests that as hGH two alternatives could be chosen, namely "polyelectrolyte complexed recombinant human growth hormone" or "human growth hormone derivative crystals". This does not appear to correspond to what is described in the description (see e.g. page 2, lines 28-30; page 14, lines 20-26; page 54, lines 23-28), leading to a lack of clarity and support (Article 6 PCT). A similar objection applies to claim 27.

3 - Adding to the lack of clarity, the term "derivative" in independent claims 1, 27 and 85 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Also the definition of this term on page 16, line 15 ff of the description, is unclear. It is unclear what is meant by a "protein that differs by at

least x % from the amino acid sequence of" hGH.
Consequently the subject-matter of claims 1, 27 and 85 does not fulfil the requirements of Article 6 PCT.
4 - The term "salt buffer", used e.g. in claim 1, is not a generally recognised term, and as such unclear (Article 6 PCT).
5 - In claim 66, the preparation of crystallized protein of claim 65 is defined as a "solution of crystals". This feature is contradictory, as a solution does not contain crystals of the dissolved compound. The same objection applies to claims 75 and 76. Claims 65, 66, 75 and 76 therefore lack clarity (Article 6 PCT).
6 - In claim 85 a lyophilized preparation is defined by its composition after resuspension. Such a definition is unclear (Article 6 PCT), as it does not define the actual lyophilized preparation. Similarly, the preparations of claims 102-123 are defined in terms of the concentration of ingredients after reconstitution. The concentrations defined cannot apply to the lyophilized preparation, leading to a lack of clarity (Article 6 PCT).

Novelty

1 - Furthermore, the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124 and 125 is not new in the sense of Article 33(2) PCT, and therefore the criteria of Article 33(1) PCT are not met.
2 - Document D1 (§§ 12-14; §§ 80-83; examples; claims) discloses crystals of human growth hormone (derivative), complexed to e.g. protamine or polyarginine, and compositions for injection comprising the crystals. A preferred formulation vehicle comprsies 100 mM sodium acetate, 5% PEG6000, 25 mM Tris.HCl, pH 7.5 (see § 83), but other formulations are foreseen (§ 82; examples 22, 25). The incorporation of the compositions in pre-filled syringes, infusion pumps and needle-free injectors is also foreseen (see e.g. § 80)
With respect to D1, claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81 and 84 are considered to lack novelty.
3 - Document D2 (examples 6-10; claims) and D3 (examples 7-10; examples) disclose the preparation of hGH crystals. After preparation the crystals are freeze-dried to achieve dry crystals, from which a pharmaceutical suspension is made. The freeze-dried crystals cannot be distinguished from the lyophilized preparation of claim 85, as they could indeed

be resuspended in a composition comprising a buffer, a salt and PEG.
Consequently, claims 85-98, 101, 124 and 125 are considered to lack novelty over D2 and D3.

Inventive Step

1 - Lacking novelty, claims 1-6, 9-11, 14, 15, 17-21, 23-25, 30, 31, 34-36, 39, 40, 42-44, 47, 48, 50, 51, 54, 65, 66, 68-71, 74-76, 78-81, 84-98, 101, 124 and 125 cannot be considered inventive (Article 33(4) PCT).

2 - Also in view of the clarity objections raised above, independent claims 27, 52, 53, 99, 100, 102-123 and dependent claims 7, 8, 12, 13, 16, 22, 26, 28, 29, 32, 33, 37, 38, 41, 45, 46, 49, 67, 72, 73, 77, 83 cannot be considered inventive. The features presented in these claims are a combination of features obvious to the skilled person in consideration of documents D1-D3, or they concern minor modifications which lie within the normal practice of the skilled person.

Industrial applicability

Claims 1-54 and 65-125 fulfill the rquirements of Article 33(4) PCT.